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<p>(21) International Application Number: PCT/US96/13500</p> <p>(22) International Filing Date: 27 August 1996 (27.08.96)</p> <p>(30) Priority Data: 60/003,277 30 August 1995 (30.08.95) US</p> <p>(60) Parent Application or Grant (63) Related by Continuation US 60/003,277 (CON) Filed on 30 August 1995 (30.08.95)</p> <p>(71) Applicant (for all designated States except US): G.D. SEARLE & CO. [US/US]; Corporate Patent Dept., P.O. Box 5110, Chicago, IL 60680-5110 (US).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): RUMINSKI, Peter, Gerard [US/US]; 391 Crestbury, Ballwin, MI 63011 (US). CLARE, Michael [GB/US]; 5154 West Brown Street, Skokie, IL 60077 (US). COLLINS, Paul, Waddell [US/US]; 1557 Hawthorne Place, Deerfield, IL 60015 (US). DESAI,</p>		<p>Bipinchandra, Nanubhai [US/US]; 200 Annapolis Drive, Vernon Hills, IL 60060 (US). LINDMARK, Richard, John [US/US]; 1165 Rue La Ville, St. Louis, MI 63141 (US). RICO, Joseph, Gerace [US/US]; 524 Weatherby Terrace Drive, Ballwin, MI 63021 (US). ROGERS, Thomas, Edward [US/US]; 755 Trago Creek Drive, Ballwin, MI 63021 (US). RUSSELL, Mark, Andrew [GB/US]; 475 Cross Road, Gurnee, IL 60031 (US).</p> <p>(74) Agents: KOVACEVIC, Cynthia, S. et al.; G.D. Searle & Co., Corporate Patent Dept., P.O. Box 5110, Chicago, IL 60680-5110 (US).</p> <p>(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</p>
<p>(54) Title: META-GUANIDINE, UREA, THIUREA OR AZACYCLIC AMINO BENZOIC ACID DERIVATIVES AS INTEGRIN ANTAGONISTS</p>		
<p>(57) Abstract</p> <p>The present invention relates to a class of compounds represented by formula (I) or a pharmaceutically acceptable salt thereof, wherein A is (a) or (b) or (c) or (d) pharmaceutical compositions thereof and methods of using such compounds and compositions as $\alpha_v\beta_3$ integrin antagonists.</p> <div style="text-align: center;"> <p>(I)</p> </div> <div style="display: flex; justify-content: space-around; margin-top: 20px;"> <div style="text-align: center;"> <p>(a)</p> </div> <div style="text-align: center;"> <p>(b)</p> </div> </div> <div style="display: flex; justify-content: space-around; margin-top: 20px;"> <div style="text-align: center;"> <p>(c)</p> </div> <div style="text-align: center;"> <p>(d)</p> </div> </div>		

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META-GUANIDINE, UREA, THIUREA OR AZACYCLIC AMINO BENZOIC ACID DERIVATIVES AS INTEGRIN ANTAGONISTS

The present application claims priority under 35
5 USC §119(e) of United States provisional application
Serial No. 60/003,277 filed August 30, 1995.

Field of the Invention

The present invention relates to pharmaceutical
10 agents (compounds) which are useful as $\alpha_v\beta_3$ integrin
antagonists and as such are useful in pharmaceutical
compositions and in methods for treating conditions
mediated by $\alpha_v\beta_3$, by inhibiting or antagonizing $\alpha_v\beta_3$
integrins.

15

Background of the Invention

Integrins are a group of cell surface
glycoproteins which mediate cell adhesion and therefore
are useful mediators of cell adhesion interactions
20 which occur during various biological processes.
Integrins are heterodimers composed of noncovalently
linked α and β polypeptide subunits. Currently eleven
different α subunits have been identified and six
different β subunits have been identified. The various
25 α subunits can combine with various β subunits to form
distinct integrins.

The integrin identified as $\alpha_v\beta_3$ (also known as the
vitronectin receptor) has been identified as an
integrin which plays a role in various conditions or
30 disease states including tumor metastasis, solid tumor
growth (neoplasia), osteoporosis, Paget's disease,
humoral hypercalcemia of malignancy, angiogenesis,
including tumor angiogenesis, retinopathy, arthritis,
including rheumatoid arthritis, periodontal disease,
35 psoriasis and smooth muscle cell migration (e.g.
restenosis). Additionally, it has been found that such
agents would be useful as antivirals, antifungals and
antimicrobials. Thus, compounds which selectively

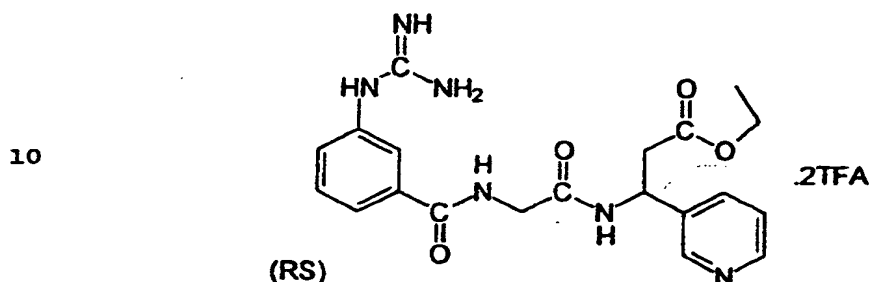
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Example 1

Preparation of (±)ethyl β-[[[2-[[[3-[(aminoiminomethyl)-
amino]phenyl]carbonyl]amino]acetyl]amino]pyridine-3-
5 propanoate, bis(trifluoroacetate) salt

Step A

15 To 3-pyridine carboxaldehyde (300 ml) in 2-propanol (3 liters) was added ammonium acetate (297 g) followed by malonic acid (398 g). The reaction mixture was stirred at reflux for 5 hours. The precipitate was filtered while hot and washed with hot isopropanol (2
20 liters). The resulting white solid was then dried to yield DL-3-amino-3-(3-pyridyl)propionic acid (220 g) as a white solid.

NMR and MS were consistent with the desired product.

Step B

25 DL-3-amino-3-(3-pyridyl)propionic acid (220 g) from Step A was slurried in absolute EtOH (3.6 liters). HCl gas (one lecture bottle - ½ lb) was bubbled into the reaction while stirring over 40 minutes (slow
30 exotherm to 61°C). The slurry was then heated at reflux for 4 hours (a solution forms after 1 to 1.5 hours). The reaction mixture was cooled to 5°C in an ice bath. After stirring at 5°C for 1.5 hours, the
35 resulting white precipitate was filtered and washed thoroughly with ether. After drying under vacuum at 50°C, the yield of ethyl DL-3-amino-3-(3-

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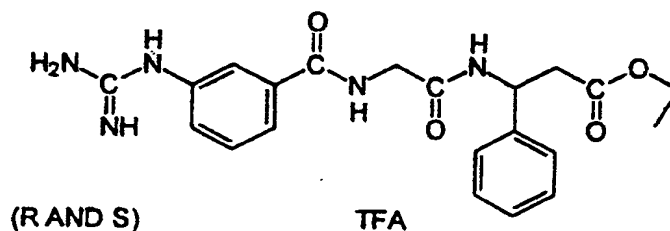
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Example 3

Preparation of (±)ethyl β-[[2-[[[3-[(aminoiminomethyl)-
5 amino]phenyl]carbonyl]amino]acetyl]amino]-
benzenepropanoate, trifluoroacetate salt

10



15 The above compound was prepared according to the methodology of Example 1, substituting an equivalent amount of benzaldehyde for 3-pyridinecarboxaldehyde in Step A.

20 NMR and MS were consistent with the desired structure.

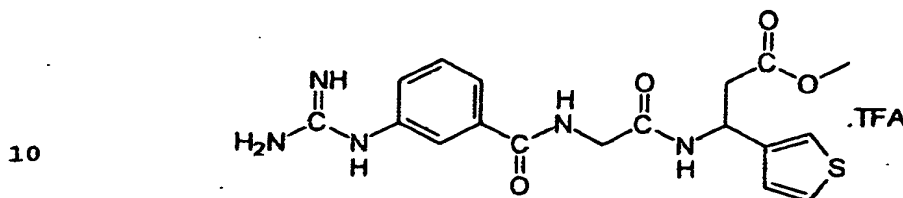
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Example 57

Preparation of (±) methyl β-[[2-[[[3-
[(aminoiminomethyl)amino]phenyl]carbonyl]amino]acetyl]-
5 amino]thiophene-3-propanoate, trifluoroacetate salt

Step A

A solution of 3-thiophenecarboxaldehyde (11.2 g)
15 in isopropanol (100 ml) was treated with ammonium
acetate (20 g). The resulting mixture was heated and
malonic acid (10.4 g) was added. The reaction was
refluxed for 4 hours and filtered while hot. The solid
was washed with hot isopropanol (2 x 50 ml) and dried
20 in vacuo overnight at 40°C. 8 g of β-aminothiophene-3-
propanoic acid was recovered. MS and ¹H-NMR were
consistent with the desired product.

Step B

25 A suspension of the product of Step A (5 g) in
methanol (100 ml) was treated with 4N HCl/dioxane (10
ml). The reaction was stirred overnight. The excess
solvent was removed under reduced pressure. Methyl
β-aminothiophene-3-propanoate hydrochloride (7.8 g) was
30 isolated as a yellow foam. MS and ¹H-NMR were
consistent with the desired product.

Step C

A solution of m-guanidinohippuric acid HCl (2.7 g)
35 in DMF (10 ml) and pyridine (10 ml) was treated with
DSC (4.5 g) and a catalytic amount of DMAP. After 4
hours, a solution of the product of Step B (2.2 g) and

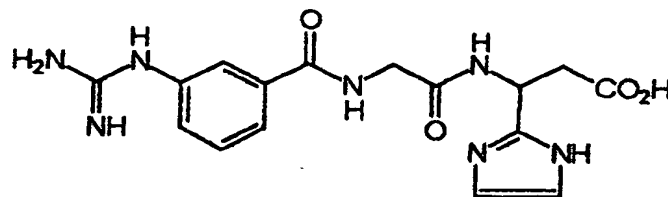
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Example 364

Preparation of (±) β-[[2-[[[3-[(aminoiminomethyl)-
amino]phenyl]carbonyl]amino]acetyl]amino]-
1H-imidazole-2-propanoic acid,
tris(trifluoroacetate) salt

Step A

A solution of 2-imidazolecarboxaldehyde (6.0 g, 0.063 mol) and (tert-butylcarbonylmethylene)triphenylphosphorane (29.4 g, 0.078 mol) in 150 mL of tetrahydrofuran was heated at 55°C overnight. The clear solution was cooled and concentrated in vacuo. The residue was purified by chromatography on silica gel (ethyl acetate/hexane, 8:2) to give 9.7 g of product (1:1 E/Z mixture) as a white solid (79%): Analysis Calc'd. for $C_{10}H_{14}N_2O_2$:

C, 61.84; H, 7.27; N, 14.42.

Found: C, 61.52; H, 7.39; N, 14.21.

25 Step B

To a suspension of prewashed sodium hydride (0.62 g, 0.026 mol) in 40 mL of dry dimethylformamide was added the product from Step A slowly. After 30 minutes, 2-(trimethylsilyl)ethoxymethyl chloride was added and the reaction mixture was stirred at room temperature for 2 hours. Water was added and the aqueous phase was extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and filtered. The filtrate was concentrated and the residue